of a study of day care workers who were exposed to PCP, PCDFs and lindane. This study found that exposed women had significantly small babies by measure of weight and length. The crude median difference between exposed and non-exposed was 175 grams and 2 cm for weight and length respectively. The differences were not explained by gestation time.[148]

Another study reports that 22 out of 90 women with histories of spontaneous abortions, unexplained infertility, or menstrual disorders were found to have elevated blood levels of pentachlorophenol and/or lindane. However, a direct causal relationship with pentachlorophenol exposure cannot be inferred from this study due to the presence of lindane in the blood and other possible confounding factors. Occupationally exposed fathers also present a risk to developing offspring. Dimich-Ward et. al. report congenital anomalies of the eye, elevated risks for developing anencephaly or spina bifida and congenital anomalies of genital organs.[149]

Neurological:

Preliminary findings in a occupational PCP exposed group revealed a significant dose-response between past exposure to PCP and reported symptoms of fever/sweating (47% in the high exposure group), weight loss (33% in the high exposure group), persisting fatigue (74% in the high exposure group), nausea (40% in the medium and high exposure groups) and responses to a screening test for neuropsychological dysfunction (Questionnaire 16) (81% in the high exposure group).[150]

like illnesses.[138] There were numerous complaints of nausea, vertigo, allergies, skin rashes, and headache.[138] A study in 1995 indicated that increased levels of PCP in blood can lead to severe T lymphocyte dysfunction. Low-level exposure to PCP is associated with abnormalities of the cellular and humoral immune parameters.[116]

Reproductive:

As early as 1975, PCP was confirmed to cross the placenta and cause teratagenic changes in rats.[144] Distinct effects on thyroid hormones were observed by Jekat.[139] A pronounced fall of circulating thyroxine (T4) and triiodothyronine (T3) levels was accompanied by lower levels of both free thyroid hormones and TSH, and the T4:T3 ratio was decreased in serum. Furthermore the intrathyroidal hormone stores were reduced. An interference of PCP at pituitary or hypothalamic level is assumed as a major mode of action.[139] Thyroid function and effects on reproduction in ewes exposed to the organochlorine pesticides lindane or pentachlorophenol (PCP) from conception was also reported by Beard.[140] PCP accumulates in growing embryonic tissue and can change the physiology of developing embryos.[145]

In humans PCP is associated with miscarriages[146] and a host of other female reproductive issues. A case control study involving women who had been exposed to wood preservatives and had an increased serum PCP values were found to affect the endocrine system at any level. PCP was suggested to act centrally on a hypothalamic or suprahypothalamic level which may results in mild ovarian and adrenal insufficiency, thereby leading to an increased infertility issue.[147] Karmaus and Wolf reported the results

Long-term low dose to Wood Processing Chemicals (WPC) and PCP was related to subjective complaints such as mood, attention, and motivation and to subtle alterations of neurobehavioral performance.[151]

A study of 214 PCP and creosote exposed individuals revealed significantly more neurophysiological abnormalities in adults in reaction time, Trails A and B, and visual field defects. Increases in self reported health effects and neurological problems were noted.[101]

Carcinogenicity:

An increased risk of cancer has been shown in some laboratory animals given pentachlorophenol orally. There is evidence that pentachlorophenol causes cancer in humans. The International Agency for Research on Cancer (IARC) has determined that pentachlorophenol is possibly carcinogenic to humans, and the EPA has classified pentachlorophenol as a probable human carcinogen.

As early as 1978, an increased risk of Hodgkin's with exposure to PCP was reported.[152] An excess risk (1.4) was found only among occupational groups with wood and paper exposure. The major difference occurred for carpentry and lumbering, with a relative risk of 4.2. The author suggested that use of PCP is common in many phases of wood processing and might be linked.[152]

Additional studies revealed that PCP was a carcinogenic metabolite[153] and PCP adducts in rats were classified as gentoxic.[154] Randerath reported that DNA damage induced in mouse tissues by organic wood preserving waste extracts[155] and Klein conducted carcinogenicity assays of wood dust and wood additives in rats exposed by long-term inhalation.[156] PCP is a potentiates adducts in adult mice.[157,158] Dahlgren et al. reported an overall increase in cancer rates in an resident population exposed to PCP and creosote.[101]

The literature on PCP exposure concerns technical grade PCP therefore some of the observed effects in humans may by in part to the presence of the impurities. For our purposes, this distinction is not necessary as all the persons in our population of interest were exposed to both PCP and dioxins (as shown by their dioxin and PCP load) (Table 10 and Table 11 and Figure 12)

Table 9. Regulatory Values for PCP.

Type	Exposure Route	Level	Based on:	Reference
ATSDR Acute MRL	Oral	0.005 mg/kg/day	LOAEL of 5mg/kg/day for developmental effects	Schwartz et al. 1974
ATSDR Intermediate MRL	Oral	0.001 mg/kg/day	LOAEL of 1mg/kg/day for reproductive effects	Beard et al. 1997
ATSDR Chronic MRL	Oral	0.001 mg/kg/day	LOAEL of 1mg/kg/day deceased serum thyroxine	Beard and Rawlings 1998
EPA Oral Reference Dose (RfD)	Oral	0.03 mg/kg/day	NOAEL of 3mg/kg/day for liver and kidney pathology	Scwetz et al, 1978
EPA Carcinogenicity		B2	Probable Human Carcinogen	
Conc. At cancer risk of 10^{-4}		0.03 mg/L		
IARC Carcinogenicity		2B	Probably carcinogenic to humans	IARC, 2001
WHO - Drinking Water Quality	Oral	9 ug/L		WHO, 2001
ACGIH TLV-TWA		0.5mg/m3		ACGIH, 2000
NIOSH REL-TWA		0.5mg/m3		NIOSH, 2001a
NIOSH IDLH		2.5 mg/m3		NIOSH, 2001b
OSHA PEL (8 hr TWA)		0.5mg/m3		OSHA, 2001b

Table 10. PCP Values in Exposed Population vs. NHANES.

ID	PCP
0053	1.0
0028	8.2
0026	nd (0.8)
0215	26
0001	1.3
0214	2.3
0007	2.0
0003	0.80
0074	2.7
0069	1.4
0088	3.4
0039	2.0
0202	2.4
0091	3.2
0050	0.80
0037	3.2
0063	nd (0.7)
0098	7.4
0065	3.4
0056	1.0
0067	2.0
0047	4.4
0082	nd (0.8)
0081	nd (0.8)

0018	2.3
0016	nd (0.8)
0030	3.8
0076	1.7
0071	19
346	1.5
NHANES 75th Percentile (non hispanic blacks)	<LOD (0.5)

Table 11. PCP levels compared to Controls.

Congener	Exposed Residents (n=29) Mean Concentration	Controls-Dallas (n=200) Mean Concentration*	NHANES 75th Percentile (95% CI)
PCP*	3.64	1.5	<LOD

*For undetectable values, half the detection limit was used for calculation purposes.

Figure 12. Chemical Structure of PCP.

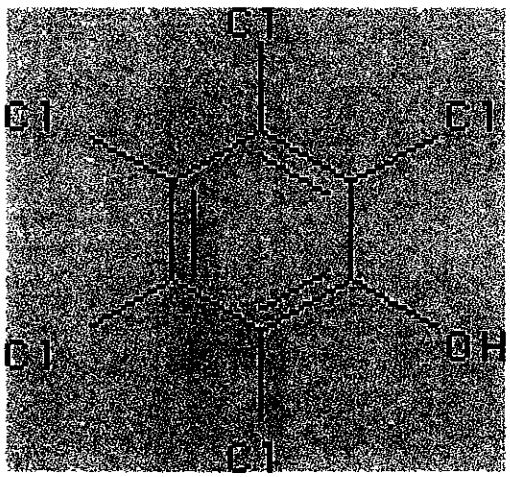
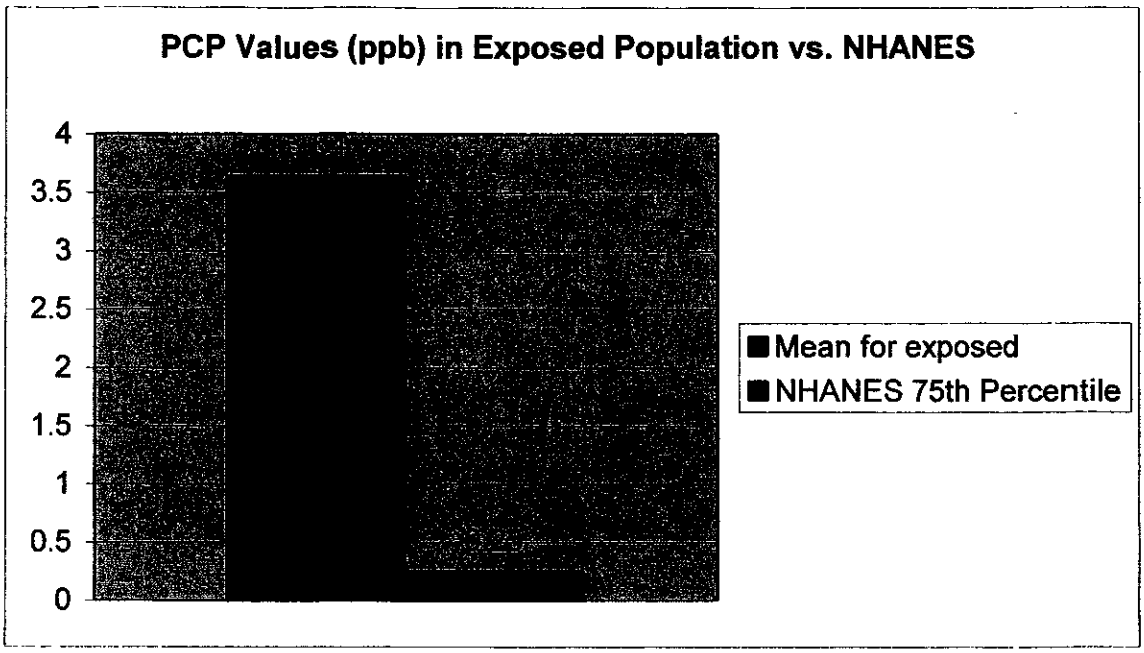


Figure 12. Histogram of PCP levels in exposed and controls.



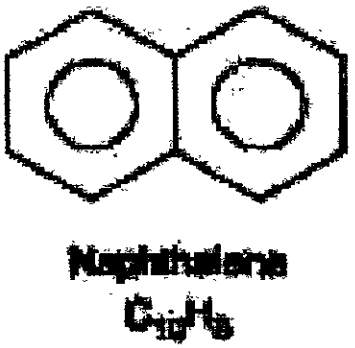
*For undetectable values, half the detection limit was used for calculation purposes.

Naphthalene:

Description

Naphthalene has been found to be carcinogenic in animal test systems and been assigned a cancer slope factor by the State of California. Naphthalene is the main constituent of creosote vapor. Naphthalene (Figure 13) is a natural constituent of coal tar, comprising approximately 11% of that material by weight.[159] Naphthalene is a white solid with a strong smell; is also called mothballs, moth flakes, white tar, and tar camphor. Naphthalene is a natural component of fossil fuels such as petroleum and coal; it is also formed when natural products such as wood or tobacco are burned. The principal use for naphthalene is as an intermediate in the production of phthalic anhydride, which is used as an intermediate in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, insect repellents, and other materials; other products made from naphthalene are moth repellents, in the form of mothballs or crystals, and toilet and diaper pail deodorant blocks. Naphthalene is also used for making leather tanning agents, and the insecticide carbaryl (Naphthalene Chemical Backgrounder).

Figure 13. Chemical Structure of Naphthalene.



Exposure Issues

Comparison of the available data indicates that, based on rough estimates of average intakes for naphthalene, most exposure occurs through inhalation. Estimated intakes from air are approximately 5 to 45-fold greater than those from food and water.[160]

Uptake and Metabolism

Naphthalene is absorbed when administered orally; although no human studies were identified that quantified the rate or extent of uptake. Dermal absorption of naphthalene in humans has been inferred from toxicity observed in human neonates who were reportedly exposed by dermal contact with clothing that had been stored with naphthalene mothballs or naphthalene flakes. Physiologically-based pharmacokinetic modeling results suggest that the inhaled naphthalene is absorbed rapidly into the blood.[160]

After distribution, naphthalene is extensively metabolized. As many as 21 metabolites (including oxidized derivatives and conjugates) have been identified in the urine of humans and animals exposed to naphthalene. The factors that influence the relative proportions of individual metabolites include species, tissue type, and tissue concentration of naphthalene. The available evidence suggests that the naphthalene metabolites 1,2-naphthoquinone and 1,4-naphthoquinone are the primary toxic species.[161]

Animal studies indicate that the majority of ingested naphthalene is eliminated as metabolites in the urine, with a small fraction eliminated in the feces.[172]

Human Health Effects

Short-Term Studies and Case Reports

There are few good studies in the literature regarding the acute effects of naphthalene exposures to humans. Ingestion of naphthalene is known to cause effects ranging from acute nausea and vomiting, to cataract formation, hemolytic anemia and death.[162,163,164,165,166]

Trans-placental distribution

Data for distribution of naphthalene or its metabolites in humans are unavailable. However, there is evidence that naphthalene can cross the placenta in humans. Erythrocyte hemolysis of sufficient magnitude to cause anemia was reported in infants born to mothers that had consumed naphthalene while pregnant.[167,168]

Sensitive Populations

Short-term inhalation exposures to naphthalene have been associated with hemolytic anemia, and occasionally, death[169] reported adverse effects in 21 Greek infants exposed to naphthalene from clothing, diapers, blankets, and other items that had been stored in contact with mothballs. Durations of exposure ranged from 1 to 7 days. Inhalation was identified as the primary route of exposure because 19 of the 21 infants did not have dermal contact with the naphthalene-contaminated materials. A total of 21 infants developed hemolytic anemia and two infants died from kernicterus, a severe neurological condition that was thought to be a consequence of massive hemolysis. Ten of the 21 anemic children and 1 of the 2 infants that died from naphthalene exposure had a genetic

polymorphism that resulted in a deficiency in glucose-6-phosphate dehydrogenase (G6PD). This enzyme helps to protect red blood cells from oxidative damage and G6PD deficiency makes the cells more sensitive to a wide variety of toxicants, including naphthalene.

Long-Term and Epidemiological Studies

There are only a few studies in the literature regarding long-term exposures to naphthalene and workers. Ghetti and Mariani (1956) reported the development of pinpoint lens opacities in 8 of 21 individuals employed for five years at a dye manufacturing plant.[170] Exposure of these workers occurred primarily via inhalation and dermal contact, but exposure levels were not mentioned. The lesions, which did not affect visual acute, were attributed to naphthalene exposure because no correlation existed between incidence and age, and because they occurred in the crystalline lens.[163]

Two epidemiological studies addressed a potential relationship between occupational exposure to naphthalene and cancer in German workers. As abstract of a case-control study by Kup described 12 cases of laryngeal carcinomas, 2 cases of epipharyngeal cancer, and one case of nasal carcinoma.[171] All but three workers were smokers. Four of the patients with laryngeal cancer also had a history of occupational exposure to naphthalene. Limitations to this study include the small number of patients studied, uncertainty about how naphthalene exposures were identified, and known exposures to other potential carcinogens. The author suggested that most of the observed cancers were probably due to non-occupational causes.[172]

The second epidemiological study reported the finding of 6 cases of cancer among 15 workers exposed to naphthalene vapors at a coal tar and naphthalene production facility.[173] The duration of exposure ranged from 7 to 32 years. Four workers developed carcinomas of the larynx. Two workers developed cancer of the stomach and cecum. All of the subjects were smokers. Limitations to this study include lack of a control population, the small numbers of workers involved, lack of quantitative exposure data, and the presence of both occupational and nonoccupational exposures to other potential carcinogens. Therefore, this study does not provide strong evidence for a relationship between naphthalene exposure and cancer incidence.[174]

No long-term studies conducted in sensitive populations were identified in the materials reviewed for this report. Because there are no reliable human studies to establish dose-response relationships for specific health effects, most dose-response information is derived from animal studies.[160]

Animal Studies

General Comments

There are a large number of studies that have been conducted in exposing animals of different species, amphibians, fish, and bacteria to varying concentrations, length of time, etc. to naphthalene. Wide variations in response to different concentrations of naphthalene are recorded. Studies in which oral exposures of lethal concentrations were conducted are of little practical value in this case. Cataract formation was one observed

result in certain animal species after a single dose of naphthalene.[174] Acute toxicity testing in rabbits revealed that 2,000 mg/kg of naphthalene causes moderate irritation (erythema, edema, and/or fissuring that resolved with 7 days) when applied directly to intact or abraded skin.[175]

Mutagenicity and Genotoxicity

Numerous *in vitro* and *in vivo* assays have been conducted to evaluate the potential genotoxicity of naphthalene and its metabolites. Until 1994-1995, the results of most studies were negative, suggesting that the genotoxic potential of naphthalene and its metabolites is weak,[172] and was probably not an area of concern for exposure to naphthalene. Studies done beginning in 1994-1995 provided significant changes to the prior scientific findings, and are discussed in the section of Carcinogenic Effects, below.

Physiological or Mechanistic Studies

Information on the mode of action of naphthalene is available for three health effects associated with exposure to naphthalene exposure: hemolysis, cataract formation, and pulmonary toxicity.[172]

Hemolysis

Humans and dogs are susceptible to naphthalene-induced hemolysis following inhalation, oral or dermal exposures. Naphthalene metabolites are believed to be involved in naphthalene-induced hemolytic anemia, but the mode of action of naphthalene induced

hemolysis is not clearly understood. Individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) are particularly sensitive to naphthalene hemolysis.[176]

Cataract Formation

Experimental evidence suggests that naphthalene cataractogenesis requires cytochrome P-450 catalyzed bioactivation to a reactive intermediate. Some evidence suggests that the ocular toxicity of naphthalene is mediated by the production of 1,2-naphthalenediol in situ in the lens.[163]

Pulmonary Toxicity

Pulmonary toxicity has been identified in experimental animals exposed to naphthalene via inhalation and parenteral pathways. The pulmonary response to naphthalene varies significantly among species. At present, there is no strong evidence that exposure to naphthalene results in pulmonary toxicity in humans.[163]

Metabolism

The metabolism of naphthalene is similar to that of many other aromatic hydrocarbons.[177,178] Initially naphthalene is oxidized by the cytochrome P450 monooxygenase system to naphthalene oxide enantiomers. The primary site of metabolism is the liver, but oxidation also occurs in the lung and kidneys. The additional metabolic steps are rather complex and beyond the immediate scope of this report.

Genotoxicity

Naphthalene has been tested for genotoxicity in a variety of *in vitro* and *in vivo* genotoxicity assays. Naphthalene has been demonstrated to induce chromosomal damage in mammalian cells i*n vitro*. The National Toxicology Program (1992)[179] found that naphthalene induced sister chromatid exchanges in Chinese hamster ovary (CHO) cells in the presence of rat liver S9 in the second of two trials and in the absence of S9 in both trials. Naphthalene also induced chromosomal aberration in CHO cells in the presence but not absence of rat liver S9. Additionally, naphthalene caused an increase in the frequency of CREST micronuclei, (indicative of chromosomal breakage) in human MCL-5 B-lymphoblastoid cells.[180] Data on the induction by naphthalene of DNA damage *in vivo* are mixed. Naphthalene has been demonstrated to have genotoxic effects in nonmammalian assay systems.[181]

Cancer Bioassays

NTP (2000) exposed groups of 49 male and female Fischer 344N (F344) rats to naphthalene by inhalation at concentrations of 0, 10, 30 or 60 ppm for 6.2 hours/day, five days/week for 105 weeks. Survival of the male and female exposure groups were similar to that of controls.

These studies found clear evidence of carcinogenic activity in male and female rats, based on increased incidences of rare tumors, respiratory epithelial adenoma and olfactory epithelia neuroblastoma of the nose, in both sexes. Respiratory epithelial

adenoma incidence occurred with a positive dose-response trend in male rats and was significantly increased in all exposed male rat groups.

Olfactory epithelial neuroblastomas occurred in males exposed to 30 and 60 ppm naphthalene and in all dose groups of naphthalene-exposed females. Neuroblastoma incidences occurred with positive response trends in males and females.[182]

Although a number of reports exist which describe non-cancer health effects in humans,[183] no studies of carcinogenic effects in humans were identified.

Naphthalene's Classification as a Possible Human Carcinogen

Naphthalene was listed as a chemical known to the State of California to cause cancer on April 19, 2002, and was classified as Group 2B (possibly carcinogenic to humans) by the International Agency for Research on Cancer in 2002 (Table 12).

California State Derivation of Cancer Potency – Risk Assessment

Unit risk values for naphthalene were calculated based on data in female mice, male rats and female rats from the studies of NTP.[178,181] U.S. EPA[160] and others have more recently advocated a benchmark dose method for estimating cancer risk.[182] This involves fitting an arbitrary mathematical model to the dose-response data. The benchmark dose methodology was applied to the tumor incidence data for naphthalene in the NTP[178,181] studies. Using this method the upper confidence bound on the unit risk value for purposes of calculating cancer risks associated with exposure to naphthalene is in the range 0.014-

0.034 $(mg/m^3)^{-1}$, based on the incidence data in female mice and female rats from the NTP[178,181] studies. The male rat was the most sensitive sex and species tested by NTP[178] in the inhalation carcinogenesis studies of naphthalene. NTP considered the increased incidences of nasal respiratory epithelial adenoma and nasal olfactory epithelial neuroblastoma, which are rare tumors, to provide clear evidence of the carcinogenic activity of naphthalene. The unit risk value of 0.034 $(mg/m^3)^{-1}$, or 3.4×10^{-5} $(ug/m^3)^{-1}$, based on the tumor incidence data in male rats, is therefore considered the most appropriate to use in risk assessment.

OEHHA's Unit Risk Value and Slope Factor

On August 3, 2004, California's Office of Environmental Health Hazard Assessment adopted a unit risk value for naphthalene of 3.4×10^{-5} $(ug/m^3)^{-1}$ and a slope factor of 1.2×10^{-1} $(mg/kg\text{-}day)^{-1}$.[182]

Environmental Fate and Distribution

Overview

Direct releases to the air account for more than 90% of the naphthalene entering environmental media.[163] The primary discharge source is residential combustion of wood and fossil fuels. About 5% of environmental naphthalene is released into water, primarily from coal tar production and distillation processes. Other contributors to water releases include effluents from wood preserving facilities and oil spills. More than half of these releases are to surface water.[163] According to ATSDR (1995), only about 2.7% of

naphthalene releases are discharged to land, but that number increased to 37% in the most recent year for which data are available –1998.[160]

Air

The primary removal process for naphthalene in air is through reactions with hydroxyl radicals. Naphthalene will also react with atmospheric N_2O_5, nitrate radicals, and ozone. The major products of these reactions are 1- and 2-naphthol and 1- and 2-nitronaphthalene. The half-life of atmospheric naphthalene is less than 1 day.[163]

Water

Naphthalene is lost from surface water via several mechanisms. Volatilization into the air is the most important route of loss from surface water.[163] Mackay and Leinonen[184] estimated a half-life of 7.2 hours for the volatilization of naphthalene (quantity not stated) from an aqueous solution 1 meter deep. Southworth estimated that a 10-fold increase in current velocity would accelerate volatilization 2 to 3 times.[185] Rodgers et al. estimated a volatilization rate constant of 0.16 $hour^{-1}$,[186] which resulted in a half-life of 4.3 hours.[160] The half-life of naphthalene in oil-polluted water versus unpolluted water is approximately 7 and 1,700 days, respectively.

Sediments

A small fraction (less than 10%) of naphthalene in water will be associated with particulate matter and will settle into sediments. Naphthalene that remains in surface

water will be degrade through photolysis and biodegradation processes. Naphthalene undergoing photolysis has a half-life of about 71 hours.[163]

Potential for Human Exposure

There are multiple exposure routes. Summary comments follow:

Drinking Water

Naphthalene was detected in both rural and urban wells of the local, State and Federal data set compiled by National Assessment Water Quality Program (NAWQP). Detection frequencies and median concentrations are low, especially for rural areas. Occurrence of naphthalene in rural areas is an order of magnitude lower than in urban areas, a trend generally observed for VOCs throughout the United States.[187]

Exposure from Food

Using the average ranges of naphthalene intake[188] an average estimated daily intake of 40.7 to 237 ng/kg-day can be calculated for a 70-kg adult, and an average daily intake of 204 to 940 ng/kg-day can be calculated for a 10-kg child. Values for individuals will vary depending upon dietary composition.

Exposure from Air

Naphthalene has been detected in indoor air samples, and residential indoor concentrations are sometimes higher than outdoor air levels. In homes with residents who smoke, indoor and outdoor air concentrations of naphthalene were reported to be 2.2

ug/m^3 and 0.3 ug/m^3, respectively.[189,190] Assuming an average ambient concentration level of 5.19 ug naphthalene/m^3 and an average inhalation rate of 15.2 m^3/day,[160] an average daily dose of 1,127 ng/kg-day can be calculated for a 70-kg adult. An estimated average daily dose of 4,515 ng/kg-day can be calculated for a 10-kg child assuming an inhalation rate of 8.7 m^3/day.[160] Individual intake will vary depending on factors including activity, geographic location, and inhalation rate.

Exposure from Soil

Chuang et al. analyzed house dust samples obtained from carpet in homes in Ohio. They reported mean naphthalene levels of 530 ug/kg (measured following Soxhetlet extraction) and 350 ug/kg (measured using sonication extraction).[191] Measurement of naphthalene concentrations in household dust were obtained from 24 low-income homes in North Carolina in 1995.[192] Concentrations ranged from <10 to 4,300 ug/kg. depending upon the location of sampling.

Low levels of naphthalene and methylnaphthalenes have been found in uncontaminated soils and sediments, while higher levels have been reported for samples taken near sources of contamination. Wild et al. reported that naphthalene levels in untreated agricultural soils ranged from 0 to 3 ug/kg.[192] Published naphthalene concentrations in contaminated soils included up to 66 ug/kg in sludge-treated soils (yu 1990), 6,100 ug/kg in coal tar-contaminated soil[193] and 16,700 ug/kg in soil from a former tar-oil refinery. For sediments, naphthalene was detected in 7 percent of 267 sediment samples entered

into the STORET (Storage and Retrieval System) database (1980 to 1982): the median concentration for all samples was reported to be less than 500 ug/kg.[194]

Humans may be exposed to soil naphthalene by inhalation of airborne soil particle, by ingestion of food-borne soil residues, by ingestion of household dust, or by direct ingestion of soil. Infants and toddlers ingest soil and household dust by hand-t-mouth transfer during everyday activities, and may therefore be exposed to higher levels of soil naphthalene than the general population.

Summary

Estimated concentration and intake values for naphthalene in media other than water have been reviewed closely. Inspection of the data reveals that, based on average intakes, most exposure occurs through inhalation, with average intakes being approximately 5- to 27-fold greater than a those from food and up to about 5-fold greater than those from soil. However, soil may be a significant route of exposure for children living in areas with soils containing high levels of naphthalene.

Synergy:

The classic synergistic model of smoking and other chemicals[195] has lead research into a new direction. Most laboratory studies have been limited to single chemicals and very little research has been done on the complex mixture of compounds that exist in the environment.[196]

The effect of exposures in the real world to a mixture of chemicals causes effects that would not be seen if the exposure was to only one compound. The assumption is that the effects of the chemicals have additive [*Additive: 2 + 2 = 4; The combined effect of the chemicals is equal to the sum of each chemical acting independently*] toxicity if they have the same endpoint.[197] In this case we see chemicals present in the community, which have similar endpoints (creosote, dioxins, polycyclic aromatic hydrocarbons, PCP, etc). These chemicals found to be present are in significant quantities that lead to an array of health effects. There is no research specifically on the mixture present in this case on which to base information about possible synergistic or potentiating effects.

Additive interactions experiments are difficult because they require extensive series of experiments that measure the potency of each chemical separately and then together. Rajapakse et al.[198,199] used weakly estrogenic compounds and ascertained that the interaction among the chemicals was additive. Rajapakse et al. state the following:

"*However, human tissues contain many compounds with estrogenic activity. On the basis of our studies, it appears conceivable that a multitude of xenoestrogens, when present in*

sufficient number and/or concentration, might in principle act together to impact on the actions of steroidal estrogens. Whether such impacts will be physiologically relevant remains to be seen. Definitive answers to this question are currently hampered by our lack of knowledge about the full spectrum of estrogenic agents in human tissues.." [198]

Therefore using the argument that a chemical is only a "weak" estrogen or "weak" promoter or "weak" initiator cannot be held unless we examine other chemicals, which might be acting together, to change the dynamics of a single compounded controlled study.

Synergism [*2 + 2 = 8*] occurs when the combined effect of two chemicals is much greater than the sum of the effect of each agent acting independently. That combination causes greater than an additive effect. Synergism is the possible reason that we find such a high rate of immune system, neurotoxic and other illnesses and health problems in this neighborhood. In addition, potentiating [*2 + 0 = 10*] effects may have played a part in the exposure as well.

The U.S. EPA guidelines for the health risk assessment of chemical mixtures involve evaluating the health effects and toxicology data on the mixture or a similar mixture. If data exist only for the components of the mixture, which is most commonly the case, the U.S. EPA guidelines recommend using an additive model for predicting risk.[160] From a medical and public health perspective, it is preferable to overestimate the risk from additive or synergistic effects than to underestimate the risk lesser health effects.

Determining these health risks from mixtures are complicated[160] because much of our understanding of health risks arise from a single dose response that can be altered to observe for disease conditions.[200] Guidelines are then set in place from establishing no oberservable adverse effect levels (NOAEL). Mechanisms for multiple chemical interactions are more complicated.[197] Chemicals can interfere with the metabolism of one another. Others may act at the cell receptor cell to either produce synergistic, additive or antagonistic effects. [196]

Miniumum Risk Limits (MRL's) are meant to help physicians and public health officials determine the safety of a community living near a substance emission. However, the MRL calculations often predict effects in adult men to only a single type of exposure. The MRL's do not take in account for how mixtures and their additive, synergistic, and potentiating effects will translate to health effects for the population at risk. Even further; women, children, the elderly, and unborn children and how they will react to these MRL levels are not addressed. Therefore long-term exposure to a mixture of chemicals within regulatory limits have lead to toxic health effects. Regulatory science rarely incorporates any interactions; it is incapable, at present, of coping with synergies.

To address such concerns, the ATSDR in conjunction with the Centers of Disease Control (CDC) have published a series of documents entitled:

1. Interaction Profile for Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX)"

2. Interaction Profile for Arsenic, Cadmium, Chromium and Lead
3. Interaction Profile for Arsenic, Hyrazines, Jet Fuels, Sontrium 90, and TCE
4. Interaction Profile for Atrazine, Deethylatrazine, Diazon, Nitrate, and Simazine
5. Interaction Profile for Cesium, Cobalt, Stronium PCBs, and TCE
6. Interaction Profile for Chloryrifos, Lead, Mercury, and Methylmercury
7. Interaction Profile for Cyanide, Flouride, Nitrate, and Uranium
8. Interaction Profile for Dioxins, Hexachlorobenzene, and PCB's in Fish
9. Interaction Profile for Dioxins, methylmercury, and PCB's in Breast Milk
10. Interaction Profile for Lead, Manganese, Zinc, and Copper
11. Interaction Profile for Trichloroethance, TCE, and Trichloroetylene

In these documents they conclude that for the most part chemical mixtures do have an additive and synergistic quality that should be investigated further. Most studies revolve around solvents, but at minimum have additive effects and in some cases have synergistic effects.

Even though the information contained with the Interaction Profiles for Dioxins and PCB's are preliminary they do provide with a very informative table. The table below is an excerpt from the Interaction Profile, which allows us to extrapolate that PCBs and Dioxins when combined result in at least an additive effect of body and organ weight changes, and decreased retinoids in liver.

A key article by Nylund et al. describe the genotoxic effects of creosote. Nylund et al. state, "*Herman et al (1980) noticed that petroleum distillate enahanced B[a]P mutagenicity at low oil doses...Further studies by Hermann (1981) showed that PAHs with 2-5 unsubsituted aromatic rings enhanced the mutagenicity of B[a]P. Low doses of naphthacene and B[e]P were found to enhance...*" The authors do state that high doses to appear to result in inhibition but the proposed mechanisms for mammals may be different that the test model of genotoxicity in vivo applied in this study.

Synergistic effects leading to tissue and organ damage is also common with mixtures of solvents including asthma, cellular toxicity and even death. Synergistic toxicity is also seen in rat models.

Several researchers have reported neurological effects in humans. Escalona et al. published a report in which neurobehavioral effects seen in workers exposed to solvent mixtures.[201] More specifically, toluene and xylene together produced neurological effects which were additive.[202] Bolla reported that a mixture of organic and inorganic lead and solvents was associated with dimished neurobehavioral performance on all the tests, which were administered. Animal studies examining synergistic models and neurological effects are abundant.[203] More recently Howard reported on neurotoxicity and showed the synergistic effects of creol-O and drusban.

Studies support the notion that solvents show association with connective tissue diseases and sclerosis[204,205] and have an additive immunotoxic effect (toluene and benzene).[206]

Other toxicology studies in chemical mixtures resulted in long-term risk of immune system issues in humans[207] and even cancer. Synergistic effects were found to produce cancer in rats and mice by low doses of amines.

Organic solvent mixtures are also associated with reduced fertility among women.[208] For example, women make their lifetime supply of eggs while still a fetus. So if a mother has exposed her female fetus to solvent exposure they are most susceptible to genetic damage during this time. In males n-hexane and toluene or xylene induced potentiating effects in the testicular tissue.[209]

Recent publications in the past few years have shed even more light on how chemical mixtures impact us. Cavieres et al. report that herbicide mixtures reduced the litter size of mice exposed to low environmentally relevant doses. The largest reductions in litter size were at the lowest dosage level used. That corresponded to EPA's "reference dose," the concentration calculated on the basis of experiments to be sufficiently low to avoid adverse health effects. This was one-seventh of the maximum contaminant level allowed in drinking water by EPA standards.[210]

Another study by Porter et al. examined the impacts on mice of different mixtures pesticides and a fertilizer at levels and in mixtures typical of drinking water in the mid-West United States. The results were that mice exposed to one compound displayed little effects where as the mixtures resulted in altered behavior and immune system function.[211]

van Birgelen et al. report synergy between a PCB congener, PCB 153, and dioxin in a rat model. PCB 153 by itself caused no increase in accumulation. Maximum increases for dioxin alone were about twice control levels. However, combining PCB 153 and dioxin caused increases 800 times above control levels.[212]

The Food Quality Protection Act of 1996 acknowledged that mixtures are the rule rather than the exception. The foundation of this Act was to require that compounds with similar mechanisms of action be considered jointly when calculating whether exposures have exceeded tolerance levels. This is a good step however the science employed is simplistic and does not address the possibility that chemicals might interact synergistically within mixtures. Synergy profoundly challenges traditional risk analysis calculations.

In conclusion, Reuter et al. states the following:

> ***"A MAK (maximum concentration at the workplace) cannot be established with a genotoxic and carcinogenic potential. Therefore, if a carcinogenic potential is proven for a mixture, even without knowledge of the carcinogenic compound, it must be categorized as a carcinogen.*** (Reuter 1996)"

Reuter et al. continue to state:

"***For complex mixtures as brown coal tar, coal tar, coal tar pitches, and coke oven emissions there is a clear epidemiological evidence of carcinogenicity. Thefore, these mixtures have been classified as III A1***. (Reuter 1996)"

Conventional regulatory toxicology begins with individual components, because of the precision with which those experiments are carried out. Real world mixtures are never considered and with the argument presented the current regulatory standards are unlikely to be sufficiently protective of public health.

Summary – Chemicals:

A creosote-coating plant was constructed near Grenada, Mississippi in 1904. The plant has been in continuous operation since that date. Ownership of the plant has changed several times. The current owner, Koppers Inc., employs approximately 60 full-time employees and produces a variety of creosote impregnated wood products.

The source of the creosote is coal-derived, and beginning in the late 1940's or early 1950's, Koppers Company began adding Pentachlorophenol to the creosote mixture to increase the longevity of the wood treatment. Typically, the wood to be treated is placed in pressurized containers where the chemicals are injected into the wood under steam pressure. Steam is generated from a boiler located nearby. For a long time the boiler's fuel was oil, however, many years ago the boiler fuel was switched to wood. The waste wood produced from the milling operations at the plant was used as boiler fuel. As production increased, and Koppers added additional plant sites, disposal of the treated wood waste became expensive. Permitting was obtained which allowed Koppers to use treated wood in their boiler at the Grenada site, officially referred to as the "Tie Plant". In order to handle the treated waste wood from the other plant sites as well as increased production, Koppers added additional boilers to the plant property.

The process of wood treatment produces waste products which are released into the air, drain from the treated wood products as liquids, or remain as solid ash. The effluents released to the air are dispersed by the ambient air currents at the time of release. The liquid wastes are drained off of stacking or drying "pads" into ditches dug into the soil,

which ultimately drain into nearby streams which in turn empty into the nearby river. For years the community near the plant obtained their drinking water from water wells on their properties. Municipal water became available many years after the community was established.

Over the years, disposal of the waste products from the Tie Plant were managed by several different methods. Initially, all ashes were placed in "ash pits" or storage piles on the plant site. Liquid wastes were allowed to enter into the drainage ditches and flow either into the ground or into the streams and nearby river. For a long time period, liquid wastes were sprayed into a holding pond where the wastes were allowed to evaporate into the air or settle into the pond sediment.

Environmental studies of the Tie Plant effluents to the air, water, and ground have identified the presence of very toxic chemicals to be present. In addition, studies reveal these chemicals to be present within the community itself. As stated in the Introduction to this report, not only have these chemicals been identified within the community environment, including individual residences, but via biochemical testing of a random sample of community residents. Studies have demonstrated the presence of these same toxic chemicals in the resident's blood as well.

The primary chemicals of concern with regard to potential effects on human health include the following:

- Coal Tar, Coal Tar Pitch, Coal Tar Pitch Volatiles & Creosote

- Polycyclic Aromatic Hydrocarbons (PAHs)
- Pentachlorophenol
- Dioxins
- Naphthalene

Coal Tar, Coal Tar Pitch, Coal Tar Pitch Volatiles & Creosote
These products are products derived from the destructive distillation of bituminous coal. Coal tar can be distilled into many fractions to yield a number of useful organic products, including benzene, toluene, xylene, naphthalene, anthracene, and phenanthrene.

Review of the medical literature associates contact with these chemical by-products with the causation of cancer. Because of the complexity of these chemicals, past medical literature contains many studies which reach inconclusive evidence of their carcinogenic nature. However, when the medical literature of these chemicals, as affects human health, are reviewed in depth, taken as a whole the medical community considers these chemicals to be directly and indirectly associated with the etiology of certain cancers in humans exposed to them. Various studies have shown a definite relationship between exposure to one or more of this chemical grouping, and cancer of multiple organs and organ systems in the body, as well as birth anomalies.

The uses of these chemical by-products from coal distillation are numerous, and this fact has contributed to the complexity of studying their potential health effects on humans. Animal studies however, confirm the carcinogenic potential of this group of chemicals, supporting the medical evidence and conclusions stated above.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are a group of over 100 different chemicals that are formed during the incomplete burning of coal, oil and gas, garbage, or other organic substances like tobacco or charbroiled meat. PAHs are usually found as a mixture containing two or more of these compounds, such as soot. Many PAHs are strong carcinogens in rodent bioassays and have been linked to increased incidences of various types of cancer in humans by the Department of Health and Human Services (DHHS). Exposures to PAHs have been demonstrated in animal studies to cause stomach cancer, lung cancer and skin cancer. High levels of PAHs fed to mice during pregnancy had difficulty reproducing.

Review of the current medical literature supports a direct causal link between exposure to PAHs and human cancers of the breast, skin, bladder, brain, lymphatic system, lung, pancreas, hematopoietic (blood forming) system, stomach, pharynx and genitourinary systems. Several studies have correlated exposures to PAHs to birth anomalies in humans.

PAHs & DNA Adducts

Transformed or activated PAHs can bind to DNA forming adducts, which is widely believed to be the initiating step in chemical carcinogenesis. Few studies have attempted to explain a dose-response relationship between environmental exposure to PAHs and PAH-DNA adduct levels. Higher PAH-DNA adduct levels are believed to predict a higher risk of cancer. Studies in animals demonstrate that the levels of DNA adducts are

related to PAH contaminated sites as compared to reference sites. Studies of Grenada community residents, as compared to non-residents, revealed the community residents to have 5.48 times higher PAH-DNA adduct levels than the comparison group.

Pentachlorophenol

Pentachlorophenol is a manufactured chemical that does not occur naturally. Pentachlorophenol is added to the wood treatment process in Koppers' Tie Plant to increase the longevity of the wood preservative process. It is widely used as a pesticide and wood preservative.

Pentachlorophenol can be found in the air, water, and soil. It enters the environment through evaporation from treated wood surfaces, industrial spills, and disposal at uncontrolled hazardous waste sites. The general populations can be exposed to very low levels of pentachlorophenol in contaminated indoor and outdoor air, food, drinking water and soil. People who work or live near a wood treatment facility or in the production of utility poles, railroad ties, or wharf pilings may be exposed to pentachlorophenol in the air or by coming in contact with the treated wood.

Humans exposed to high levels of pentachlorophenol can experience severe effects including liver damage and damage to the immune system. In humans, PCP is associated with miscarriages and multiple other female reproductive issues. Long-term exposure to low levels of PCP in humans can cause damage to the skin, liver, kidneys, cardiovascular, immune and nervous systems. Damage to the thyroid, endocrine, immune, and reproductive systems has been observed in laboratory animals exposed to long-term

exposure to low levels of pentachlorophenol. It is not known if exposure to pentachlorophenol will result in birth defects or other developmental effects in humans. Death, low body weights, decreased growth, and skeletal effects have been observed in laboratory animals exposed to high levels of pentachlorophenol during development. There is weak evidence that pentachlorophenol causes cancer in humans and is classified as a Class 2B carcinogen (possible human carcinogen) by the International Agency for Research on Cancer (IARC).

Dioxins

Dioxins are a class of chemicals of 75 different compounds. These compounds have far-reaching toxic effects, many of which are unknown as yet. The most studied of the class is 2,2,7,8-tetrachlorodibenzo-p-dioxin, or 2,3,7,8-TCDD. The various dioxins have different levels of toxicity depending upon how toxic they are found to be in various test systems. These compounds are known to interact chemically with specific chemical receptors within cells, which interfere with the function of cellular DNA. Dioxins are produced from the Koppers wood treating process as they are contained in the creosote and pentachlorophenol used to treat the wood and are released to the environment during the production cycles.

Importantly, the diseases which have been linked to dioxin seem "endless". TCDD has been classified as a known human carcinogen by IARC since 1997. Epidemiology data have shown increases in soft tissue sarcomas, respiratory system tumors and all cancers combined. TCDD is a carcinogen in all species of laboratory animals tested, with tumors detected in the liver, thyroid, respiratory tract and other organs and tissues.

Ingesting dioxin can also result in congenital malformations, spontaneous abortions, and a slow wasting syndrome followed by death similar to the AIDS syndrome. Dioxin exposure causes damage to the urinary and hematological systems, growths in the colon, gall bladder, multiple myeloma, and lung, larynx and prostate cancer. According to ATSDR, a government agency, dioxin's health effects include endocrine disruption, reproductive impairment, infertility, birth defects, lowered sperm counts, impaired neurological development, damage to the kidneys, and metabolic dysfunction.

There is no evidence there is a safe level of dioxin exposure below which none of these effects will occur. The Minimum Risk Level (MRL) set by the government (ATSDR) for dioxin is the lowest MRL of any chemical. This level, 1x10-6 ug/kg/day of dioxin is thought to be safe for a 22 pound (10 Kg) 2 year old human to ingest per day is 10 picograms. A picogram is one quintillionth of a gram. There are 454 grams in a pound. The pictogram is 0.000000000000001 grams. This is a small quantity and is probably exceeded in the case of the children who live on Carver Circle, next to the Koppers Plant.

Naphthalene

Naphthalene is a natural constituent of coal tar as well as fossil fuels, and is also formed when natural products such as wood or tobacco are burned. Available data indicate most exposure to naphthalene occurs through inhalation. Naphthalene is a by-product of Koppers Tie Plant wood treating process.

Exposure to high levels of naphthalene is highly toxic to both humans and animals. There are few human health studies on the effects of exposure to low levels of naphthalene. Recent evidence indicates it is a possible human carcinogen, and is classified by IARC as a Group 2B carcinogen in 2002.

Summary – Health Effects:

Pancreatic cancer

A risk factor for pancreatic cancer is the PAHs in cigarette smoke.[213] This risk factor is associated with 25 – 27% of pancreatic cancer cases.[214,213] Ojajarvi et al.[215] report their findings of a meta-analysis of pancreas cancer and occupational exposures. The authors were careful to include only those studies that met high epidemiologic standards for study design and analysis. They found an increased risk from occupational PAH exposure. Every study included in the meta-analysis that reported on PAH, found increased rates of pancreatic cancer in PAH exposed populations. The "meta-" etiological fraction among the PAH exposed is 33%. In other words, among those who were exposed to PAHs and have pancreatic cancer, the PAH exposure accounts for 33% of the cases.

Nevertheless, there is certainly enough published epidemiologic data to confirm that PAH exposure causes or contributes to pancreatic cancer. However, it must be noted that some of the same authors who report positive associations discount their own findings because of the lack of statistical significance,[215] others do not.[216] However, when the number of positive studies adds up to four, five and six as reported by in Ojajarvi's meta-analysis.

Stomach cancer

Cigarette smoking is associated with stomach cancerl.[217] It has long been suspected that PAH is a cause of stomach cancer.[48,47] Dusich reported significantly increased rates of gastrointestinal tract cancer in creosote exposed women suggesting a possible association.[36] In LaDou's most recent edition Harrison points out the occurrence of

stomach cancer in PAH exposed populations.[50] Randem et al. found increased rates of stomach cancer in asphalt workers.[218] Dioxin has also been implicated in the etiology of stomach cancer.[86] A Japanese study showed an increase in stomach cancer with creosote ingestion used to treat stomach upset.

Breast cancer

Coal tar creosote, PAHs and dioxins have all been implicated in the etiology of breast cancer. Although there have been studies published with negative findings,[37,219] the majority of published studies have indicated a causal relationship between breast cancer and the chemicals of interest here[36,220,59,221,222,43] and several authors have determined that there is suggestive or conclusive evidence indicating causality and/or cancer promotion for PAHs and dioxins;[59,221,220] yet we have more work to do in order to clearly understand the mechanisms of action.[221] In addition, the research suggests that some known risk factors for breast cancer may in fact modify the effect of these chemicals. For instance, Rundle et al. suggest that the effect of PAHs on breast cancer is mediated by alcohol consumption for those who are genetically predisposed. Current drinkers who were genetically predisposed had higher levels of PAH adducts compared to nondrinkers with the same genetic profile.[220] It is also worth noting that TCDD is both a cancer initiator and promoter, a notion supported by Steenland et al. in their large cohort mortality study.[85]

Diabetes

Dioxin is known to cause diabetes. The soldiers exposed to Agent Orange in Viet nam have an increase in diabetes. This is suggestive of a threshold effect, in other words, after minimal exposure, those who were susceptible developed the disease and the others never did. In fact, most studies that report on blood glucose concentrations and rates of diabetes in dioxin-exposed cohorts find increases in the occurrence of diabetes.[90]

Liver condition

LaDou's *Occupational and Environmental Medicine*, "elevated liver enzymes have been found in a group of coke oven workers heavily exposed to PAHs, and excess mortality from cirrhosis of the liver has been observed in a cohort of workers heavily exposed to chlorinated naphthalenes." Kogevinas, in his recent review of the health effects of dioxin, asserts that temporary increase in liver enzymes is a proven effect of dioxin.[90]

Cardiovascular Disease

Steenland et al. found a modest but significant trend of increasing SMR with increasing exposure to TCDD.[85] Additionally, an internal analysis comparing non-exposed plant workers to those with varying degrees of exposure reveals a robust exposure-response trend with the highest exposure group showing a rate ratio of 1.75 (95% CI = 1.07 – 2.87). The most disturbing finding was the lack of latency. It appeared that the heart disease occurred simultaneously with exposure. The authors note that the persistence of TCDD in tissue could result in long-term cardiovascular health effects. High blood pressure, congestive heart disease and heart murmur are all complications of ischemic

heart disease. Increased systolic blood pressure and heart rate has been demonstrated in PCP-exposed workers.[141]

Asthma

The increased risk of asthma has been documented in worker in the asphalt industry [218] and associated with coal tar creosote exposure in both children and adults.[101] Outdoor air pollution is associate with upper and lower respiratory symptoms.[223] Polycyclic organic matter, pentachlorophenol and naphthalene have all been identified in the clean air act as hazardous air pollutants.[224] Both children and adults have been shown to experience increased frequency and severity of asthmatic symptoms with increased measures of air pollutants.[224]

The evidence that environmental tobacco smoke (ETS) has a causal role in asthma-related morbidity is sufficiently strong.[225] To our knowledge, the possible synergistic effects of PAH, PCP, naphthalene or other exposures concurrent with environmental tobacco smoke have not been addressed. However, because they share some of the same constituents it is likely that these exposures would be even more damaging when coupled with ETS.

Chronic bronchitis and increased rates of obstructive lung disease have been associated with PAHs.

Dental problems

There is ample evidence in the literature to support the assertion that dioxin damages teeth in rodents when exposed both in vitro (embryonic teeth),[93] after birth (young adult rats)[91] and by lactational exposure.[92] One of these studies also found diminished skull size with dioxin exposure.[91] Jan and Vbric found dramatic dental defects in children with PCB exposure and they postulate that the mechanism of action is similar to TCDD.[96]

Birth effects

Perera et al report smaller birth size among newborns with PAH-DNA adducts above the median ($3.85/10^8$ nucleotides).[66] Although fetal exposure to PAH is less than maternal exposure,[67] the fetus is apparently unable to clear the substance or repair the damaged DNA.[69] Birth weight, length and head circumference are lower in newborns with high leukocyte levels of PAH-DNA adducts. Reduced head circumference is inversely related to PAH-DNA adducts both before and after birth weight was included in the model suggesting asymmetrical growth retardation. Reduced head circumference of 1 – 2 centimeters in newborns has been associated with reduced *mental and psychomotor development* in early childhood[70,71] and head circumference is correlated with brain size, *intelligence quotient, and cognitive function.*[72] Similar findings birth weight less than 2500 grams, gestation less than 37 weeks, and poor 5-minute Apgar scores were found in creosote residents in addition to anomalies of the respiratory system, genital organs, poly/syndactyly, clubfoot, musculoskeletal, and of the skin hair, and nails.[219] PCP has been linked to reduced weight and length in newborns.[148] And, according to the ATSDR, dioxin also causes birth defects.

Conclusion:

My studies of the residents living near the Koppers Plant indicate that these residents have been exposed to harmful chemicals and that this exposure has adversely affected their health. The above review reveals that the plaintiffs have been exposed to chemicals known to cause the types of health problems that they have. To a reasonable medical and scientific certainty, the plaintiffs' have been exposed to a significant amount of toxic chemicals for many years. The health effects from their exposures are serious and require extensive treatment both in the past and in the future.

Patient Reference List:

Most of the health effects that are seen in these plaintiffs were reported in my paper published in Environmental Research in 2004 so I have not included that reference in each patient to avoid repetition.

Kay Hobbs

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